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EXAMINER	
MACFARLANE, STACEY NEE	
ART UNIT	**PAPER NUMBER**
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,346	NAKAGAWARA ET AL.	
	Examiner	Art Unit	
	Stacey MacFarlane	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *1 and 4-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/31/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 2 and 3, in the reply filed on November 19, 2007 is acknowledged. The traversal is on the ground(s) that the claimed subject matter can and should be searched together and that the restriction requirement set forth by the Office "does not seem to reflect consideration of the economic penalty foisted on Applicant(s)". Furthermore, Applicant asserts that the restriction requirement is flawed in that it pre-maturely applied new rules that did not go into effect as per the U.S. District Court injunction. These arguments have been fully considered but are not found persuasive for the following reasons. Examiner maintains that there is a lack of Unity of Invention among the structurally and functionally distinct agents and drugs and methods employing said agents, as set forth for reasons of record in the Restriction Requirement filed October 18, 2007. The agent of Groups 1 contains c-Abl and/or $p19^{ARF}$, the agent of Group 3 contains AICD, and the agent of Group 4 comprises the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2. These agents are each structurally distinct and are not so linked in structure or function as to convey Unity of Invention among them as a single group. The agent of Group 7 requires inhibition of the interaction between AICD and p53, the agent of Group 8 inhibits the interaction between AICD and Fe65 in neurons, and the agent of Group 9 inhibits the interaction between AICD and Tip60. These are each functionally distinct physiological effects and there is nothing of record to indicate that there is a structure, function, or structure-to-function correlation between the agents of Groups 7-9 so as to

convey Unity of Invention. Furthermore, the following reference teaches that recombinant c-Abl was known in the art prior to filing, thus teaching the agent of Claim 1 (Donaldson et al. PNAS, 99(22):14053-14058, October 2002).

2. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1 and 4-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 19, 2007.

4. Claims 2 and 3 will be examined upon their merits in the instant office action.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 2 is vague and indefinite for its recitation of the acronym (AICD) that is not spelled-out in its first use in the claims. Within the art the term AICD is known to stand for both "APP intracellular C-terminal domains" and "Apoptosis Induced Cell Death", so one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claims. It would be remedial to define the acronym in claim 2 so that it is clearly understood what it stands for.

8. Claim 2 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: there are no active steps recited by which the screening method is to be performed.

9. Claim 3 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the active steps by which "an AICD/p53 complex is formed together with a candidate drug"; the active steps by which the first and second immune complexes are formed; the active steps within the "step of detection"; the active steps by which a "cell lysate" is formed; and the resulting step whereby the candidate drug is selected as a drug for the prevention and/or treatment of Alzheimer's disease. Specification indicates some of the active steps that appear to be missing (¶ 0108). The claimed methodology seems to be drawn to a disruption of a protein-protein interaction such as an immunoprecipitation complex between AICD and p53, however, as recited the metes and bounds of the screening method are not clearly delineated so that one of ordinary skill in the art would be reasonably apprised of the encompassed subject matter.

10. The term "inhibits the interaction between AICD and p53" in both claims 2 and 3 is a relative term which renders the claims indefinite. The term "inhibit" is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree. Thus, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 2 and 3 broadly encompass methods of screening by which a candidate drug which inhibits the interaction between AICD and p53 in neurons is selected for the prevention and/or treatment of Alzheimer's disease. Claims 2 and 3 are single means claims in that they recite a screening method wherein any candidate drug which inhibits the interaction between AICD and p53 is selected as a drug for the prevention and/or treatment of Alzheimer's disease. Candidate drugs are defined in the instant specification as "nucleic acids, proteins, other high molecular weight compounds, and low molecular weight compounds (chemically synthesized or natural)" (¶ 0097). MPEP 2164.08(a) defines a single means claim as a claim which covered every conceivable means for achieving the stated purpose when the specification disclosed at most only those means known to the inventor (specifically SEQ ID NO: 1 and SEQ ID NO: 2 of the disclosure). This type of claim was held to be nonenabling for the scope of the claim in *In re Hyatt* , 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983) because the specification disclosed at most only those means known to the inventor. When claims depend on a recited property (i.e. disruption of and interaction), a fact situation comparable to Hyatt

is possible, where the claim covers every conceivable structure or means for achieving the stated result while the specification discloses at most only those known to the inventor. This appears to be the instant case and the claims are not commensurate in scope with the specification. Applicant should note that the claims are so broad as to encompass such things as a generic protein synthesis inhibitor, anything that alters cellular metabolism, or any agent that results in cell death of the cultured neurons, which is inhibition taken to the extreme.

The invention is based on the following hypotheses: (1) that a physical interaction exists between AICD and p53 (Figures 15 and 18 of the specification); (2) that this interaction is relevant to the etiology of Alzheimer's disease; and (3) that any drug that can disrupt this protein interaction would be a drug useful to treat and/or prevent Alzheimer's disease. As it is stated by Applicant, "according to the present invention, a drug/agent for the prevention and/or treatment of Alzheimer's disease having a mechanism of action which is different from that of, for example, an anti-amyloid antibody or beta- or gamma-secretase inhibitor can be developed, and new options for the prevention and/or treatment of Alzheimer's disease are therefore made available" last sentence of specification. However, the claim covers every conceivable mechanism of action for achieving the stated result, disruption of binding between AICD and p53. The instant specification does not provide clear method steps by which the method is to be performed (see above section 6), nor does it provide enough guidance or direction in the form of working examples to demonstrate evidence that a nexus between the etiology of Alzheimer's disease and an AICD/p53 interaction exists. Thus,

there is no indication that any candidate drug that inhibits this interaction would successfully treat and/or prevent Alzheimer's disease, as claimed. Absent such guidance, one of ordinary skill in the art would require undue experimentation to discover how to practice Applicant's invention as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The nature of the invention relates to the screening of candidate drugs which inhibit the interaction between AICD and p53. The state of the art at the time of filing recognized that cleavage of APP by beta- and gamma-secretases not only generates the pathological amyloid peptides but also release APP intracellular c-terminal domains (AICD) that cause apoptosis in cells (Kinoshita et al. Journal of Biological Chemistry, 277: 28530-28536, 2002). It was also known in the art that wild-type APP but not familial Alzheimer's disease (FAD) mutant APP was known to inhibit p53 DNA-binding activity and gene transactivation (Xu et al. Proceedings of the National Academy of Sciences, USA, 96:7547-7552, 1999). It was also known that APP-BP1, an APP binding protein that specifically interacts with the c-terminal of APP, is necessary for induction of the p53-mediated apoptosis pathway (Chen et al. Journal of Cell Biology

163(1): 27-33, October 2003). Taken together these studies indicate that a putative interaction between p53 and AICD was well known in the art prior to filing.

With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the scope of enablement, the claims are analyzed with respect to the teachings of the specification and are to be given their broadest reasonable interpretation that is consistent with the specification. See MPEP 2111 [R-1], which states: "During patent examination, the pending claims must be "given *>their< broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550- 51 (CCPA 1969)".

As such, the broadest reasonable interpretation of the claimed method is that any candidate drug comprising "nucleic acids, proteins, other high molecular weight compounds, and low molecular weight compounds (chemically synthesized or natural)" that inhibits the interaction between AICD and p53 in neurons is selected as a drug for the prevention and/or treatment of Alzheimer's disease. Thus, the claims encompass an unreasonable number of structurally distinct compounds and mechanisms of inhibition, many of which, for example, general protein translation or DNA synthesis inhibitors, have no association with the specific pathology of Alzheimer's disease and would not

reasonably be useful drug for the prevention or treatment of the disease. As opposed to the claims, what is disclosed about the claimed method is narrow: The working examples on pages 22-25 of the specification provide no guidance as to a method comprising the specific steps of Claim 3, and further seem to indicate that cisplatin is needed for the induction of endogenous p53, which is absent from the claims. There is no evidence of record to indicate that there is a nexus between the interaction of AICD and p53 and the etiology of Alzheimer's disease (AD), thus, one of ordinary skill in the art would not reasonably expect that administration of the drug would have any effect on AD. Furthermore, claims are drawn to screening for drugs that prevent AD and as the following reference indicates, there are no effective treatments that reverse, slow down, or prevent the progression of Alzheimer's disease (page 1 of Vickers, *Drugs Aging*, 19(7):487-494, 2002). Therefore, the disclosure provides no guidance as to how to use the invention as claimed.

While the skill level in the art is high, the level of predictability is low. As stated above, an interaction between p53 and AICD had long been suggested prior to filing, however as the following reference indicates, much unpredictability remains with respect to research aimed at elucidating a p53 and AICD connection (Alves da Costa et al. The Journal of Neuroscience, 26(23):6377-6385, June 2006). Alves da Costa et al. demonstrate that an indirect connection exists in that expression levels of AICD influence expression levels of p53 (Figure 1) that AICD induces caspase and p53 activity (Figure 3), and that cell confluency can confound the results (page 6378, paragraph 1, last line), but the study indicates that no physical interaction exists directly

for AICD and p53 but rather AICDC59 physically interacts with the p53 promoter (Figure 3F). Furthermore, there is no evidence within the art to suggest that such interactions play a role in the etiology of Alzheimer's disease.

Applicant's invention is predicated on the hypothesis that any compound that inhibits the interaction between AICD and p53 will be a useful candidate drug for treatment or prevention of Alzheimer's disease. The standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use with a reasonable expectation of success. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentech, Inc, v. Novo Nordisk*, 42 USPQ 2d 1001, (CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution.

Conclusion

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacey MacFarlane whose telephone number is (571) 270-3057. The examiner can normally be reached on M,W and ALT. F 6 am to 3 pm, T & R 5:30 am - 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/SNM/

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PRIMARY EXAMINER